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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,768	09/28/2001	Derek Van Der Kooy	Bereskip & Parr	6817

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/966,768	VAN DER KOOY ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *25-27,30,48 and 49* is/are allowed.

6)☐ Claim(s) *1-11,14-24,28,31-47,50* is/are rejected.

7)☒ Claim(s) *12,13 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Non-Final Office Action is a response to the "Response to the Examiner's Action..." (Paper No. 8) and "Declaration of Drs. Derek van der Kooy and Vincent Tropepe" (Paper No. 6) filed 6 March 2003 in reply to the Non-Final Office Action mailed 28 August 2002 (Paper No. 5). Claims 1-46 were considered in Paper No. 5. Claims 1, 2, 9, 10, 13, 14, 17, 19, 20, 25, 28-30, 33, 36, 37 and 39-46 were amended and claims 47-50 were added in Paper No. 8. Claims 1-50 are pending and under consideration.

Priority

Applicant argues persuasively that the limitations of claims 8, 9 and 33-40 are adequately supported by the provisional application. In addition to the passages cited by Applicant, claims 33-40 are further supported in the provisional application at page 3, lines 14-18. Therefore, the claims will be afforded a priority date of 29 September 2000.

Claims 4-7, and 43-46 are denied benefit of the provisional application for reasons of record and herein below in the "Response to Arguments".

Response to Arguments

Claims 4-9, 33-40 and 43-46 were denied benefit of the provisional patent for reasons of record in Paper No. 5. In response to the denial of priority, Applicant cites the *Guidelines for the Examination of Patent Applications under 35 USC 112, paragraph 1, Written Description Requirement* (66 FR 1099) and generally argues that the subject matter of the claim need not be described literally in order for the disclosure to satisfy the description requirement. Applicant

argues, claims may be supported in the specification through express, implicit or inherent disclosure and the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those in the art that, as of the filing date, applicant was in possession of the invention as now claimed.

With regard to claims 4-7, Applicant argues that the teachings found at page 9, lines 25-29 support the claimed subject matter. However, as applicant points out, the cited passage explicitly sets forth a preferred embodiment of low cell density as a range of densities between 1 cell/μl and 50 cells/μl, and, more preferably, a density of 20 cells/μl. The M.P.E.P. instructs, "[w]ith respect to changing numerical range limitations, the [written description] analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure" and cites *In re Wertheim* (191 USPQ 90) in which the court held that a claim reading literally on embodiments outside of a range described in the original specification does not meet the description requirement (M.P.E.P. 2163.05 III.). In the instant case, the portion of the range between 0 and 1 cell/μl is clearly not inherent to a range of densities between 1 cell/μl and 50 cells/μl, as low cell density is defined in the provisional application. Therefore, the claims are not supported by the provisional application. With regard to claim 7, directed to the method wherein the cell density is 10 cells/μl, the original disclosure does not provide an explicit or implicit recitation of 10 cells/μl; therefore, the limitation is not supported by the provisional application.

With regard to claims 43-46, applicant appears to be arguing that the claimed subject matter is inherent to the teachings of the provisional application. That is, the claim limitations are subgenera of the genera set forth in the provisional application. The U.S. CCPA has held that "it

cannot be said that subgenus is necessarily always implicitly described by a genus encompassing it and a species upon which it reads" (*In re Smith*, 173 USPQ 679 (CCPA 1972)). Claims 43-46 are directed to methods of supplying cells for treatment of and methods of treatment comprising administering cells. In support of these claims, applicant points to teachings related to using the cells for the development and testing of drugs for treating developmental and cerebral neural anomalies and neuropathies, and related to embryo transfer of stem cells. As neither of these teachings contemplate therapeutic administration of cells, they clearly do not support the subject matter claimed in claims 43-46.

Response to Amendment

Specification

Objection to the specification is withdrawn.

Claim Objections

Objection to claims 9, 46 and 14 are withdrawn.

Claim Rejections - 35 USC § 101

Rejection of claims 25-27 and 39 under 35 U.S.C. 101 as directed to nonstatutory subject matter is withdrawn.

Claim Rejections - 35 USC § 112, first paragraph

Claim 17 stands rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for reasons of record in Paper No. 5 and herein below in the "Response to Arguments".

Rejection of claims 31, 33-35, 37, 38, 40 and 41 under 35 U.S.C. 112, first paragraph, as lacking adequate written description is withdrawn in view of the arguments of record in Paper No. 8.

Rejection of claims 1-19, 28, 29 and 37-46 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter is withdrawn.

Rejection of claims 20-23 under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter is withdrawn.

Claims 44-46 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for reasons of record in Paper No. 5 and herein below in the "Response to Arguments".

Claim Rejections - 35 USC § 112, second paragraph

Rejection of claims 17-19 under 35 U.S.C. 112, second paragraph, as indefinite is withdrawn.

Claim Rejections - 35 USC § 102

Rejection of claims 4 and 5 under 35 U.S.C. 102(a) as being anticipated by Tropepe et al. (April 2001) *Neuron* 30: 65-78 is withdrawn in view of the statements in the Declaration (Paper No. 6).

Rejection of claims 25, 26, 29-31 and 39 under 35 U.S.C. 102(b) as anticipated by Fraichard et al (1995) *J. Cell Sci.* 108:3181 and claims 25, 26 and 29-32 under 35 U.S.C. 102(b) as anticipated by Okabe et al. (1996) *Mechanisms of Development* 59: 89-102 is withdrawn in view of the amendment of the claims such that they are directed to an isolated "primitive" neural stem cell. On page 15, lines 21-22, the specification defines the primitive neural stem cells of the invention as LIF-dependent cells. In contrast, Fraichard *et al.* and Okabe *et al.* do not detect neural precursor cell markers until after LIF is withdrawn.

Rejection of claims 33-40 rejected under 35 U.S.C. 102(b) as being anticipated by Tropepe et al (1999) *Soc. Neurosci. Abstracts* 25: 527 is withdraw in view of the claims now being afforded benefit of the provisional application filing date.

Response to Arguments

Claim Rejections - 35 USC § 112, first paragraph

Claim 17 was rejected because the disclosure does not provide adequate written description for the broad class of *any* and *all* inhibitors of TFG-β-related signaling. In response, Applicant has amended the claim such that it now refers to "TGF-β superfamily signal

transduction". Applicant first submits that the application includes more written description than was identified in the previous Office Action and cites references set forth in the specification which describe the Cerberus family of proteins. Applicant's point is taken insofar as it constitutes adequate written description for the Cerberus family. Applicant states that the application describes a significant number of inhibitors of TGF-β signaling and provides a representative number of species. This argument has been fully considered but is not found persuasive because it does not acknowledge the enormous scope and diversity of compounds encompassed by the inhibitor of the claim. As stated in the previous office action, the genus of inhibitors would comprise a diverse set of compounds from antagonists of TGF-β receptor binding, to general inhibitors of kinase and other signaling molecules. Even taking into account the Cerberus family, the disclosure provides this group of structurally related compounds and Noggin as the only examples of inhibitors of TGF-β superfamily signaling. Given that the TGF-β superfamily comprises several distinct receptors which could signal through a variety of pathways, the inhibitor of the claim encompasses all molecules that could act as antagonists of each receptor, and selective or non-selective inhibitors of each molecule participating in the signaling pathway activated by each receptor. A disclosure of Noggin and the Cerberus family of proteins is clearly not representative of such a diverse set of compounds.

Applicant next argues that, "[t]here is no requirement to disclose common structural characteristics that confer on Noggin and Cerberus the function of an inhibitor of TGF-β related signaling. The Applicants may disclose any sufficient combination of relevant, identifying characteristics, such as structure or other physical and/or chemical properties." This argument is not persuasive because, although the characteristics set forth for Noggin and Cerberus proteins

might identify other Noggin- or Cerberus-like proteins, they would clearly not identify the many inhibitors of TGF-β superfamily signaling that are structurally unrelated to Noggin or Cerberus. The relevant identifying characteristics must identify the genus, not the species set forth as examples.

Applicant argues that inhibitor of TGF-β superfamily signaling are "readily identified through articles and assays in the art. As well...any compound that is an inhibitor of TGF-β related signaling is useful according to the claimed invention, irrespective of its structure" (page 11). Applicant asserts that the relevant art is not unpredictable in view of the teachings in the application and cites disclosed results that indicate inhibition of the TGF-β related signaling is sufficient to enhance primitive neural stem cell colony formation. Applicant states, "[t]he results provide a strong basis to assert the usefulness of any inhibitor of TGF-β related signaling" (page 112). However, Applicant is reminded that the claim is rejected because the disclosure fails to adequately *describe* inhibitors of TGF-β superfamily signaling, not because the disclosure fails to teach how to use said inhibitors. As pointed out in the previous office action, *Vas-Cath Inc. v. Mahurkar* (19USPQ2d 1111) makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). Therefore, for reasons of record, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of inhibitors of TGF-β signaling. Therefore, only the described Noggin and Cerberus family members meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 44-46 were rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for treatment of a neurodegenerative disorder. In response, Applicant argues that the skilled artisan in possession of the instant primitive neural stem cells would rely on teachings in the specification and general knowledge in the art with respect to transplantation of cells to treat neurodegenerative disorders and diseases resulting from cell loss or function in the neural system. Applicant cites the chimera data in Figure 6 as an example of how the primitive neural stem cells can be transplanted. Applicant then argues that the primitive neural stem cells are the best candidate cell type to transplant because the cells are not an aggregation of different neural and non-neural cell types. Applicant asserts that the primitive neural stem cells will respond to the appropriate environment. These arguments have been fully considered but are not found persuasive. Applicant is arguing that, because the instant cells are an improvement over the cells available in the art, the claimed methods of treatment are enabled. The previous office action cites teachings from the art which indicate that, at the time of filing, successful treatment of neurodegenerative diseases using stem cells was highly unpredictable and that even success in animal models was not an indicator of success in human therapy. As the art does not teach how to use stem cells to treat neurodegenerative diseases, and indicates that such treatment is unpredictable, the skilled artisan must rely on the teachings in the specification to provide sufficiently detailed disclosure of the claimed method such that it can be practiced without undue experimentation. Given that even animal transplantation models are not considered reliable predictors, the instant disclosed method of embryo transfer clearly cannot be taken as evidence of enablement for a method of treating neurodegenerative disorders through transplantation of

primitive neural stem cells into the damaged or degenerating nervous system of an adult animal or human.

Applicant also cites several studies as examples of successful transplantation; however, even the authors of these studies do not assert that their findings indicate enablement for treatment of neurodegenerative disorders through stem cell transplantation. Brustle *et al.* teaches, "[t]he efficient generation of ES cell-derived glial cells and their use in a neonatal myelin disease model indicates that this strategy *might eventually* be applicable to human neurological disorders. Although cell replacement in adult inflammatory myelin diseases such as multiple sclerosis *poses additional problems*, further optimization of the donor ES cells...may help to meet these challenges" (page 756, column 1; emphasis added). Thus, Brustle *et al.* teaches that there is more work to be done before the methods disclosed therein could be applied to the clinic. Yang *et al.* teaches, "neural stem cells, if grown under appropriate conditions *in vitro* and transplanted into a suitable environment *in vivo*, possess the remarkable ability to spontaneously develop into neuronal-like cells, express traits of a DA phenotype, and integrate into the host brain. While this represents a major step forward in the quest to differentiate stem cells into neurons of a specific class, *many important matters remain to be resolved before contemplating use of these cells in the treatment of neurological disorders...*" (page 59, column 1; emphasis added). This teaching clearly indicates that the art does not recognize successful engraftment of neural stem cells in an animal model or expression of a phenotypic marker of differentiation as evidence that methods of treating neurological disorders using stem cells are enabled. Benninger *et al.* teaches that the methods set forth therein could be used for several purposes, including: morphological analysis; study of neurodegenerative diseases; study of neural repair; or study of

neuroregeneration or neurodegeneration (page 339, column 2). Benninger *et al.* does not even contemplate using the disclosed method to treat a disease; and, given the teachings cited in the previous office action and the passages quoted above from the art cited by Applicant, the skilled artisan would not predict that the teachings of Benninger *et al.* could be adapted for treatment of a neurodegenerative disease without undue experimentation. Likewise, McDonald *et al.* does not suggest that the methods disclosed therein could be used to treat a disease in a human. The art of record clearly fails to teach how to use stem cells to treat a neurodegenerative disease in humans, as is encompassed by the instant claims, and indicates that, at the time of filing, the teachings of the instant disclosure could not be further developed to provide successful treatment of a neurodegenerative disease without undue experimentation. Therefore the claims stand rejected.

New Grounds

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim1-11, 14-24, 28, 31-38, 40-43, 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for differentiating one or more pluripotent embryonic stem cells to primitive neural stem cells or secondary primitive neural stem cell colonies, or a method for screening for modulators of primitive neural stem cell differentiation wherein the cells are cultured in medium comprising LIF, does not reasonably provide enablement for the methods wherein the medium does not comprise LIF. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The amended claims are directed to methods of making or using primitive neural stem cells. Although the claims encompass methods wherein the primitive neural stem cells are produced in the absence of LIF, the specification states at page 15, lines 21-22 that the novel primitive neural stem cells of the invention are distinguished in that they are LIF dependent cells. Thus, it would appear from the teachings of the specification that the cells cannot be produced in the absence of LIF. Therefore, the claims are not enabled for methods of producing primitive neural stem cells, as such cells are identified in the specification, in the absence of LIF.

Claims 39 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to an isolated modulator or differentiation factor detected by the methods of claims 33-37 and a method of using said modulator or differentiation factor. The modulator or differentiation factor of the claims encompasses a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function has not been defined. In the absence of such a relationship either disclosed or in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition. The fact that one could have assayed a

compound of interest using the claimed assays does not overcome this deficit since one would have no knowledge beforehand as to whether or not any given compound would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Claims 39 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As described above, the claim encompasses a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function has not been defined. An adequate written description of a molecule requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the molecule itself. It is not sufficient to define molecule solely by its principal biological property, i.e., it functions as a modulator or differentiation factor, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any molecule with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all molecules that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is

an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). With respect to the method claims, adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences, which provide the means for practicing the invention.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of modulators or differentiation factors encompassed by the claim.

Claim Rejections - 35 USC § 102

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 33-40 are rejected under 35 U.S.C. 102(a) as being anticipated by Tropepe *et al.* (1999) *Soc. Neurosci. Abstracts* 25: 527.

The art is applied to the claims as set forth on pages 13-15 of Paper No. 5. Although the claims are now afforded a priority date of 29 September 2000, Tropepe *et al.* anticipates the claims according to 35 U.S.C. 102(a) as it is a publication by another. Although the Declaration provided states that Sirard did not contribute to the concepts disclosed in Tropepe *et al.* (April 2001) *Neuron* 30: 65-78 which read on the claimed subject matter, the Declaration does not address the contribution of Sirard to the Tropepe *et al.* (1999) disclosure. A similar statement

regarding the contribution of Sirard to the Tropepe *et al.* (1999) disclosure would overcome this rejection.

Allowable Subject Matter

Claims 25-27, 30, 48 and 49 are allowed.

Claims 12, 13 and 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
May 12, 2003

JAMES KETTER
PRIMARY EXAMINER